Issues in Clinical Child Psychology

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Adherence to Pediatric Medical Regimens

Third Edition

Springer

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Series Editor

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Michael A. Rapoff, Ph.D.

To my wife, Kim, who I always love, therefore I always need.

To our children, Lindsey and Nathan, and Grandchildren, Harrison and Elliott, our hope for the future and the joys of our lives.

In loving memory of my mother, Shirley Rapoff, for making all her six children feel special.

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Preface

Medications don't always work like they should, transplanted organs are rejected, bacteria develop resistance to previously effective antibiotics, and physicians are hampered in their ability to judge the efficacy of treatments they have prescribed. What factors could account for these alarming trends in medicine? One significant factor is that patients and their families don't always adhere to prescribed treatments. Why this is the case and what can be done about it is the subject of this book.

Before proceeding with the discussion of medical adherence in pediatrics, several caveats are in order:

1. *It is incumbent on medical providers that they are asking patients to adhere to regimens with demonstrated efficacy*. Providers need to remind themselves of the Hippocratic Oath: "I will follow that system of regimen which, according to my ability and judgment, I consider for the benefit of my patients, and abstain from whatever is deleterious and mischievous" (as cited in Cassell, 1991, p. 145).

   Providers need to be adherent to established treatment guidelines. For example, interventions have been tested that targeted improvements in adherence to asthma treatment guidelines by providers (Okelo et al., 2013)
2. *Providers need to abandon the "blame and shame" approach to dealing with medical adherence problems*. It is tempting to blame patients for adherence failures and shame them into changing their behavior. Providers need to share the blame (or better yet omit blame) and look at their own attitudes and behaviors which impact adherence. For example, failing to simplify regimens or minimize negative side-effects can adversely impact patient adherence.
3. *Patients and their families are no longer (or maybe were never) satisfied with a passive role in their health care*. In fact, the term "compliance" lost favor in the literature because it implied for some an authoritarian approach to health care that required unquestioned obedience by patients to provider recommendations (Dimatteo & DiNicola, 1982; Vrijens et al., 2012). Comprehensive and effective health care requires a cooperative relationship between providers and patients and their families. It also acknowledges the following realities, particularly for treating persons with chronic illness:

> Doctors do not treat chronic illnesses. The chronically ill treat themselves with the help of their physicians; the physician is part of the treatment. Patients oversee themselves. They determine their food, activity, medications, visits to their doctors – most of the details of their own treatment. (Cassell, 1991, p. 124)

4. *Finally, children are not little adults*. Pediatric adherence issues are arguably more complex than with adults because of the influences of family members and peers. There are also developmental processes and constraints that uniquely affect adherence for children and adolescents. Caution is in order when extrapolating from theoretical and empirical work with adults and applying this information to pediatric patients.

This volume is intended to give primary and allied healthcare providers, researchers, and students an overview of the topic of medical adherence in pediatrics. Chapter 1 reviews definitions of adherence, types of adherence problems, and adherence rates to regimens for chronic diseases. Chapter 2 is a review of the consequences of nonadherence and correlates of adherence. Chapter 3 reviews and critiques adherence theories, such as self-efficacy theory, and the clinical implications of these theories. Chapter 4 reviews developmental factors related to assessing and improving adherence (a new chapter for this edition). Chapter 5 describes and critiques different measures of adherence such as assays, electronic monitoring, and self-reports. Chapter 6 reviews measures of disease and health status measures, such as quality of life (this chapter has been separated from the chapter on adherence measures from the previous edition, as this is a growing topic and deserves a chapter of its own). Chapter 7 summarizes and critiques adherence intervention studies for chronic pediatric diseases including meta-analyses of pediatric adherence intervention studies. Chapter 8 is a review of educational, organizational, and behavioral strategies for improving adherence. Chapter 9 review ways to improve pediatric medical adherence research, such as using single-subject designs, minimizing attrition, and calculating effect sizes and documenting clinical significance/social validity (a new chapter for this edition). Chapter 10 concludes the book with a review of cultural, ethical, and legal issues related to adherence clinical and research activities (also a new chapter for this edition).

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Contents

Chapter 1
Definitions of Adherence, Types of Adherence Problems, and Adherence Rates

The Problem of Adherence

A 10-year-old boy with asthma presents in the emergency room looking pale, is having extreme problems in breathing, and is admitted to the intensive care unit. After several days, his asthma is stabilized and he is sent home. This pattern has been repeated several times over the past several years for this boy. The boy and his mother report that he "usually" takes all his prescribed inhaled and oral medications to treat his asthma and rarely misses a dose. His pulmonary function test results, his frequent visits to the emergency room, and his repeated hospitalizations would suggest otherwise.

Health professionals are all too familiar with the above scenario. There is now over five decades of research documenting that nonadherence to medical regimens is common and persistent problem (averaging around 50% with regimens for chronic diseases). Medical nonadherence can compromise the effectiveness of healthcare treatments, as well as the overall health and quality of life of youth with chronic health conditions (DiMatteo, 2004; DiMatteo et al., 2002; Fredericks et al., 2008; Kvarnström et al., 2018; McGrady & Hommel, 2013). Medication nonadherence is further associated with increased healthcare utilization and substantially higher healthcare costs (Hommel et al., 2017; Sokol et al., 2005). This chapter will review how adherence has been defined, the types of adherence problems young people experience, and the studies reporting on adherence rates to regimens for chronic diseases.

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Definitions

The term "adherence" is preferred over compliance because it better reflects a more active role for patients and their families in consenting to and following prescribed medical regimens and treatments (Lutfey & Wishner, 1999; Vrijens et al., 2012). Adherence has been defined as "...the extent to which a person's behavior (in terms of taking medications, following diets, or executing lifestyle changes) coincides with medical or health advice" (Haynes et al., 1979, pp. 1–2). This is historically the most widely quoted definition in the literature and retains its usefulness because it specifies several important elements related to adherence:

- *Specific behaviors are required of a prescribed medical regimen*. Patients are asked to do specific tasks, e.g., take medications and follow diets.
- *Adherence is not a dichotomous, all-or-nothing phenomenon*. There are qualitative and quantitative differences in adherence. For example, nonadherence to medications can take many forms, such as never filling the prescription, omitting doses, doubling up on missed doses, and even overdosing.
- *There can be concordance or lack of concordance between what patients are asked to do and what they actually do* (if their behavior "coincides" with advice they are given). This implies that there is a standard for judging whether adherence is acceptable or not.

While the "standard" for nonadherence has been somewhat arbitrary across the literature and varies widely between different chronic disease groups (e.g., Dracup & Meleis, 1982; Osterberg & Blaschke, 2005), a taxonomy approach with standard definitions has been proposed by Vrijens et al. (2012). This taxonomy for patient medication adherence relies on two key elements:

- *Adherence to medications* is the process by which patients take their medications as prescribed. Adherence to medication is comprised of three phases, including initiation, implementation, and discontinuation of medications:
  - *Initiation* occurs when the patient takes the first dose of a prescribed medication.
  - *Implementation* is the extent to which a patient's actual dosing corresponds to the prescribed dosing regimen, from initiation until discontinuation.
  - *Discontinuation* occurs when the patient stops taking the prescribed medication.
- *Management of adherence* is the process of monitoring and supporting patients' adherence to medications by healthcare systems, providers, patients, and their social networks.

In 2003, the World Health Organization updated the previous definition of adherence (Haynes et al., 1979) to incorporate the importance of the patient-provider relationship. The adherence literature identifies the *quality* of the treatment relationship between the patient and healthcare provider as an important determinant of

adherence (e.g., Rand, 1993). Effective patient-provider treatment relationships are characterized by an atmosphere in which alternative therapeutic options are discussed and the medical regimen is negotiated and agreed upon. Thus, the World Health Organization agreed upon the following definition of adherence: "the extent to which a person's behavior – taking medication, following a diet, and/or executing lifestyle changes, corresponds with agreed recommendations from a health care provider" (World Health Organization, 2003, pp. 3–4). This definition was further updated in 2005 by the National Coordinating Centre for NHS to define *Intentional* and *Unintentional* nonadherence (Horne et al., 2005). These definitions of nonadherence focus on the concept that agreement to follow a prescribed medical regimen has been secured from the patient. In pediatrics, the agreement to follow a prescribed regimen must also be obtained from caregivers, particularly for younger children.

The World Health Organization (2003) definition of adherence is consistent with a more patient- and family-centered approach to adherence that acknowledges that patients and their families make an initial decision to follow a prescribed regimen and make the decision to sustain adherence over time. The three-phase taxonomy proposed by Vrijens et al. (2012) defines the initiation of medication as *primary adherence*. The second and third phases of medication adherence (implementation and discontinuation) are defined as *secondary adherence*. Secondary nonadherence has been the focus of most research studies and is used frequently as a quality measure for clinical trials and pharmacy reimbursement. In contrast, primary medication nonadherence (e.g., not filling prescription) has been highlighted as a gap in the medication adherence literature (Adams et al., 2004; Cheen et al., 2019).

The World Health Organization (2003) definition of adherence further places the responsibility on healthcare providers to explain treatment options and to negotiate with patients and families on what they are willing to do (Adams et al., 2004). However, how much healthcare providers can negotiate with patients and families without compromising the standard of care is an ethical and potentially legal dilemma. If they compromise care by agreeing to a less intense regimen and the child has a bad outcome, the healthcare provider may open themselves to a lawsuit. Also, while adolescents can and should take part in negotiations, there is uncertainty regarding how much younger children can be involved. Children up to 11 years of age do not always understand the value of preventive medications and find it difficult to understand why someone should take medications when they are not feeling sick (Sanz, 2003). For example, they may not understand why inhaled steroids should be taken to control inflammation for asthma especially when they are not experiencing any breathing problems.

When reading this book, a clear definition of chronic disease (versus acute illness) must also first be established. This book adopts the following definition of chronic disease: a disease that is permanent; has long-term consequences; causes some level of disability; is caused by nonreversible pathological alteration; requires special training of the patient for treatment and/or rehabilitation; or may require a long period of supervision, observation, or care (World Health Organization, 2003).

Types of Adherence Problems

There are qualitative as well as quantitative differences in adherence. For medications, families may not even fill a prescription given to them by a healthcare provider (primary nonadherence), or they may not refill it in a timely fashion or never refill (secondary nonadherence). Patients may miss or delay doses in a variety of ways. For example, if patients do not take any medications for 3 or more consecutive days, this has been labeled a "drug holiday" or "treatment intermission" (Tibble et al., 2020; Urquhart & De Klerk, 1998). The possible consequence of taking treatment intermissions is that there is a decline in drug concentrations and actions, and if the delay is long enough, the actions can completely fade away. For example, in an animal model of epilepsy, a 2-week period of nonadherence to carbamazepine was associated with significant reductions in seizure control; however, these effects were reversible with restarting the medication (Thomson et al., 2017). In adolescent renal transplant patients, treatment intermission occurred in 28.6–45.5% of patients, with nonadherence leading to kidney rejection in some cases.

Another commonly described phenomenon is "white-coat adherence." This is when patients increase their adherence to medications just prior to a scheduled clinic visit, due to the social desirability effects of wanting to look adherent to their medication regimen (Driscoll et al., 2016; Modi et al., 2012; Urquhart, 1994). If drug assays are obtained at a clinic visit, it may appear that the patient has been adherent consistently because most drugs have plasma half-lives that are less than 16 hours, when in fact the measured plasma level only reflects dosing in the prior 48 hours or less, the peak time period for white-coat adherence (Urquhart, 1994; Urquhart & De Klerk, 1998). With the increased availability of electronic medication monitoring (see Chap. 5), recent studies have begun investigating treatment intermissions and white-coat adherence patterns among youth with chronic diseases.

White-coat adherence has been documented in pediatric patients with asthma (Keemink et al., 2015), type 1 diabetes (Driscoll et al., 2011, 2016, 2017; McConville et al., 2020), and epilepsy (Modi et al., 2012). In one study examining white-coat adherence in youth with asthma, a subgroup of patients (15.4%) were documented to increase their adherence to inhaled corticosteroids in the month following a clinic visit. Several studies have noted white-coat adherence in type 1 diabetes. Both younger children and adolescents with type 1 diabetes tend to engage in increased frequency of blood glucose monitoring, carbohydrate counting, and delivery of insulin boluses for the 1- to 2-week period before a clinic visit compared to prior weeks (Driscoll et al., 2011, 2016, 2017; McConville et al., 2020). In pediatric patients with epilepsy, Modi et al.' (2008) pilot study of 35 pediatric patients found that children did not demonstrate white-coat adherence during the first month of treatment. However, in Modi et al. (2012) larger longitudinal study examining medication adherence over a 13-month period in 120 children with newly diagnosed

epilepsy, children demonstrated increased white-coat adherence during the 3 days preceding their neurology clinic visits over time. Children with epilepsy further demonstrated increased variability in their medication adherence over time. These studies emphasize that medication adherence is variable among pediatric patients and their parents, tends to change over time, and is not a static outcome.

Another qualitative distinction in the literature is whether nonadherence is intentional or unintentional nonadherence (Horne et al., 2005). Examples of unintentional nonadherence include forgetting to take medications, missed dosages due to changes in family routines, low income and lack of resources to obtain or refill medication, and misunderstanding how to carry out a specific regimen (Adams et al., 2004; Klok et al., 2015; Lehane & McCarthy, 2007; Wu et al., 2018). Even in pediatric leukemia treatment where motivation is high, unintentional nonadherence is not uncommon (Mancini et al., 2012). It is also possible that nonadherence to prescribed regimens may be strategic, rational, and adaptive in certain cases (Deaton, 1985). This type of nonadherence has been described as "intentional," "volitional," "educated," and "adaptive" nonadherence (Adams et al., 2004). Intentional barriers to adherence are common and are often driven by patient or family perceptions of the child's illness, beliefs about medications, avoidance of medication side effects, and/or a deliberate choice not to follow the provider's medical recommendations (Klok et al., 2015; Mancini et al., 2012). Intentional nonadherence is common in youth with chronic medical conditions (e.g., Hodges et al., 2020; Morton et al., 2014; Schober et al., 2011) and is driven by a variety of reasons. For example, in a study of youth with diabetes, youth reported intentional insulin overdosing due to wanting to engage in binge eating, intentional self-harm accompanying stress or suicidal ideation, attempt to gain attention from parents, and wanting to feel high with hypoglycemia episode (Schober et al., 2011). Youth reported insulin underdosing or omission due to patient denial of diabetes in situations with peers, fear of a severe hypoglycemia episode, and intentional weight reduction.

The historical "culture of medical practice" rests on the assumption that patients or their parents seek medical advice and will follow this advice with reasonable fidelity (Vandereycken & Meermann, 1988). Yet medical treatments sometimes have serious side effects or do not produce anticipated outcomes, or patients find more acceptable substitutes. Studies in both youth and adult patients with HIV (Heath et al., 2002), epilepsy (Brodtkorb et al., 2016; Tang et al., 2013), sickle cell disease (Fogarty et al., 2022; Hodges et al., 2020), and other chronic diseases (Konstantinou et al., 2020) document intentional nonadherence due to negative medication side effects or fear of negative medication side effects, such as severe physical symptoms (e.g., loss of hair, pain, fatigue, jaundice) and feelings of depression on the medication. Other reasons why patients or families may intentionally not adhere are that their treatment goals are different from their provider and the prescribed treatment does not fit into their lifestyle (Adams et al., 2004; Konstantinou et al., 2020).

Adherence Rates to Chronic Disease Regimens

There is wide variability in adherence rates depending on the patient sample and disease, what regimen component is being assessed (e.g., medications, diet, or exercise), how adherence is assessed, and the criteria sometime used to classify patients as adherent or nonadherent. Global estimates are that adherence averages between 50 and 75% for youth with chronic disease regimens (Burkhart & Sabate, 2003; Rapoff & Barnard, 1991). However, there is considerable variability in adherence rates for chronic disease regimens depending on the disease, regimen requirements, measure of adherence, and the criteria for classifying patients along adherence dimensions (see Table 1.1).

Table 1.1 summarizes adherence rates and methods of adherence measurement for the most common pediatric chronic diseases (see Supplemental Reference List for additional articles that contributed only to Table 1.1). Across studies, prescribed medical regimens varied from medication only to combined medication and healthy lifestyle (i.e., diet, exercise) to diet only (e.g., celiac disease). Methods of adherence measurement varied widely across studies, as well as the operational definition of adherence for each study (e.g., <90% versus <60% of medication use equaled nonadherence; subtherapeutic versus nondetectable assay level equaled nonadherence). The most common method of adherence measurement was parent and/or child report. However, many studies used objective measures of adherence such as electronic monitoring, pill count, pharmacy refill records, and direct observation. For some chronic diseases (e.g., asthma, cancer, GI disorders, rheumatic conditions), blood and urine assays were used to measure medication or diet adherence. Many studies used a combination of methods to assess adherence, which is recommended because there is no single gold standard for measuring adherence (Quittner et al., 2008).

Several conclusions can be drawn in reviewing the studies that contribute to Table 1.1. Adherence rates are highly variable among and between different measures of adherence, with biological measurements not always correlating with objective measurements (e.g., Cain et al., 2020; Creary et al., 2020). Adherence rates tend to be higher by parental or youth reports versus more objective measures of adherence such as assays or electronic monitoring. Also, adherence to regimens tends to decrease over time for youth with asthma (e.g., Arcoleo et al., 2019; Jónasson et al., 2000), cancer (e.g., McGrady & Pai, 2019; Tebbi et al., 1986), celiac disease (e.g., Pedoto et al., 2020; Sbravati et al., 2020), cystic fibrosis (e.g., Hommel et al., 2019; Rouzé et al., 2019), diabetes (e.g., King et al., 2014; Kovacs et al., 1992; Leggett et al., 2019; Niechciał et al., 2020), epilepsy (e.g., Lee et al., 2016; Smith et al., 2018), and even solid organ transplantation (Dew et al., 2009). Adherence also tends to be higher to medication regimens versus other nonmedication regimens, such as diet, exercise, and other self-care regimens (e.g., Narayanan et al., 2017; Psihogios et al., 2020; Yawn et al., 2016). Of all the disease categories, adherence is relatively higher for medication regimens for HIV/AIDS, which makes sense in that this is a more imminent life-threatening disease. Although

Table 1.1 Adherence rates by diseases, type of regimens, and adherence measure

	Medical regimens	Adherence rates			Types of Measurement		
Chronic disease		Report measures	Objective measurement	Biochemical measurement[a]	Report measures	Objective Measurement	Biochemical Measurement
Asthma	Inhaled steroids Inhaled beta-agonist Metaproterenol Theophylline Other asthma control strategies (e.g., buying a mattress cover, following action plan)	3–66%	17–87%	10–66%	Parent report Daily diary	Electronic monitor Canister weighing Counting remaining doses in inhaler Medication possession ratio Pharmacy claims	Serum assay Urine assay
Cancer	Prednisone Penicillin/antibiotics Trimethoprim/ sulfamethoxazole 6-Mercaptopurine	32–90%	40–95%	33–98%	Parent report Child report Provider report	Electronic monitor Medication possession ratio	Serum assay Urine assay
Cystic fibrosis	Medications Antibiotics Nebulized medications Inhalation therapy Chest physiotherapy Vitamins/enzymes Diet	22–100%	42–86%		Parent report Child report Daily diary Dietary recall Provider report in chart	Device utilization data Electronic monitor Medication possession ratio Pharmacy refill	

(continued)

Table 1.1 (continued)

	Medical regimens	Adherence rates			Types of Measurement		
Chronic disease		Report measures	Objective measurement	Biochemical measurement[a]	Report measures	Objective Measurement	Biochemical Measurement
Diabetes (type 1)	Blood glucose monitor Insulin Diet Exercise Other diabetes self-care tasks	6–95%	10–99%	34–69%	Parent report Child report Provider report Structured interview	Electronic monitor Pill count Blood glucose meters Observation Medical chart review	HbA1c monitor
Epilepsy	Benzodiazepines Anticonvulsant and antiepileptic medications Ketogenic diet	28–98%	22–87%	22–86%	Parent report Structured interview	Electronic monitor Medication possession ratio Pharmacy refill Medical chart review	Serum assay Saliva assay
GI disorders (celiac, IBD, Crohn's)	Aminosalicylates Thiopurines TNF inhibitors Recombinant human erythropoietin injections Gluten-free diet Enteral nutrition Vitamin & mineral supplements	30–97%	34–97%	19–96%	Parent report Child report Food diary Provider report Structured interview	Electronic monitoring Pharmacy refill Pill count Stopped treatment	Biopsy Serum assay Breath test

HIV/AIDS	Antiretroviral medications	44–95%	41–96%	44–94%	Parent report Child report Recall interview Semi-structured interview	Electronic monitor Medical chart review Pharmacy refill Pill count Clinic visit	Viral load serum assay Plasma drug concentration
Rheumatic diseases (JIA, lupus)	Penicillamine Hydroxychloroquine Immunosuppressive drugs TNF inhibitor Corticosteroids Nonsteroidal anti-inflammatory drugs Salicylates or naproxen Exercises Splints/wraps	53–95%	26–97%	64%	Parent report Child report Provider report	Electronic monitor Pharmacy refill Pill count Medical chart review	Serum assay
Sickle cell disease	Hydroxyurea Antibiotics Medications Immunizations Transcranial Doppler Other self-care requirements	13–100%	12–98%	33–96%	Parent report Child report Daily diary Nurse report Provider report Medical chart review	Electronic monitor Medical record review Medication possession ratios Pharmacy refill Pill count Video observation	Serum assay Urine assay

(continued)

Table 1.1 (continued)

	Medical regimens	Adherence rates			Types of Measurement		
Chronic disease		Report measures	Objective measurement	Biochemical measurement[a]	Report measures	Objective Measurement	Biochemical Measurement
Spina bifida	Bowel medications Catheterization Diet Exercise Skin checks	53–98%			Parent report Child report		
Transplantations	Immunosuppressive drugs Medications Diet	49–98%	57–98%	50–84%	Parent report Child report Daily diary Provider report Nurse report	Electronic monitor Pill count	Serum assay Plasma assay Medication level variability index Coefficient of variation

Note: [a]Subtherapeutic or negative biochemical values

it is difficult to aggregate adherence rates across or within disease categories, low adherence to medical regimens remains a significant problem which can threaten the health and well-being of young people with chronic diseases.

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